Remarks

Withdrawal of the finality of the last office action, the objection to the specification and the rejections under 35 U.S.C. § 112, first paragraph (new matter) and 35 U.S.C. § 112, second paragraph is appreciated.

Claim 3 has been amended to include the limitations of claim 4. Claim 4 has been cancelled.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-6 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Table 8 illustrates 1) that each of SEQ ID NO:15, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, or SEQ ID NO:14 binds to osteoprogenitor cells and significantly increase cellular attachment over the control and 2) antibodies to integrins (i.e., $\alpha_v\beta_3$) inhibit the percentage of attached cells and cell spread induced by the peptides (i.e., SEQ ID NO: 15), indicating that the peptides interact with integrins.

The Examiner suggests that the data demonstrating the binding of SEQ ID NO: 15 to $\alpha_v\beta_3$ in Table 8 cannot be extrapolated to SEQ ID NO: 11 (or any other osteopontin derived peptide) binding any integrin on any cell type. However, due to the **sequence similarity** between the peptides and the presence of the required motifs recognized by integrins, one of ordinary skill in the art would have a reasonable expectation that peptide fragments of

osteopontin (i.e. SEQ ID NO: 11) other than SEQ ID NO: 15 would bind to integrins, such as $\alpha_v\beta_3$.

For example, the amino acid sequences for SEQ ID NO: 11 and SEQ ID NO: 15 are shown below with similar residues in bold.

SEQ ID NO:11 **RSRRATEVFTPVVPTVDTYDGRGDSVVYGRRSKSKKFRRP**AGAAGGP AGPAGPAGPAGPAGPA (63 amino acids)

SEQ ID NO: 15- acetyl-**RSRRATEVFTPVVPTVDTYDGRGDSVVYGLRSKSKKFRRP** (40 amino acids)

A Blast 2 Sequence comparison (attached- 2 pages) shows that the two sequences have a high degree of similarity (score), and two NCBI Conserved Domain BLAST searches (attached- 3 pages each) demonstrate that both SEQ ID NO: 11 or SEQ ID NO: 15 have conserved domains similar to osteopontin, which binds to a number of integrins, including $\alpha_v\beta_3$ (Hu et al. *J. Biol. Chem.* 270 (44): 26232-26238 (1995) ("Hu"), submitted with Applicant's Amendment and Response of May 11, 2004).

Integrins are the principal receptors on animal cells for binding most extracellular matrix proteins, including collagen, fibronectin, and laminin, thus, they are found on the surface of numerous cell types (see, for example, *Molecular Biology of the Cell.* IV. Cells in Their Social Context. 19. Cell Junctions, Cell Adhesion, and the Extracellular Matrix, Garland Publishing (1994)). Although the specification uses osteoprogenitor cells as an example, one of ordinary skill in the art would know that the osteopontin-derived peptides of this invention would be able

to interact with integrins (i.e., $\alpha_v\beta_3$) found on diverse cell types, such as those recited in claim 6. As an example, the Applicants have attached Horton, MA. *Int. J. Biochem. Cell. Biol.* 29(5): 721-725 (1997), which states that $\alpha_v\beta_3$ expression has been shown *in vivo* in osteoclasts, platelets and megakaryocytes, kidney, vascular smooth muscle cells, endothelium, and placenta. The reference also states that $\alpha_v\beta_3$ expression is up-regulated in certain pathologies, such as malignant melanoma, and in **numerous** *in vitro* cultured adherent cell lines (see section entitled "Biosynthesis and Tissue Distribution" on page 722). Therefore, one of ordinary skill in the art would know that there is a reasonable expectation of success that the osteopontin fragments would increase cell attachment and spreading of other cell types other than osteoprogenitor cells.

The Examiner alleges that SEQ ID NO: 15 or any other fragment of osteopontin will not bind to CD44 and α_v β1 because osteprogenitor cells were able to attach and spread in the presence of antibodies against CD 44 and α_v β1. However, one can not come to that conclusion from the data presented, because the assay described in the specification is **not** a binding assay. All that one can deduce is that CD44 and $\alpha_v\beta_1$ are 1) either weakly expressed or not expressed by osteoprogenitor cells and/or 2) osteopontin fragment-induced cell migration and cell spread in osteoprogenitor cells preferentially occurs through an integrin (i.e., $\alpha_v\beta_3$) or integrins other than CD44 and $\alpha\beta_1$. See, for example, Noonan KJ et al. J. Orthop Res. 14(4): 573-81 (1996) (abstract submitted with Applicant's Amendment and Response of May 11, 2004), which describes that reduced expression of CD44 was observed in osteoprogenitor cells compared to other bone-related cell types.

The other papers submitted with the Applicant's Amendment and Response of May 11, 2004, Tuck et al. *J. Cell Biochem* 78(3): 465-475 (2000) ("Tuck") and Hu (cited above), clearly support this rationale. Tuck demonstrates that different integrins are involved in the osteopontin-induced migration of three mammary epithelial cell lines (see Abstract and Results section on page 469). Tuck shows that the migration of two of the cell lines (21PT and 21NT) is blocked with antibodies against $\alpha_v\beta_5$ and β_1-integrin, but **not** with antibodies against $\alpha_v\beta_3$, while the migration of the third cell line (MDA-MB-435) **is** blocked with antibodies against $\alpha_v\beta_3$. If one uses the Examiner's reasoning to analyze the results of the 21PT and 21NT cell lines, one would come to the erroneous conclusion that osteopontin does not bind $\alpha_v\beta_3$, when in fact, it is well known in the literature that osteopontin does indeed bind to this integrin (see the Introduction of Hu, especially the 2nd paragraph).

There is no legal requirement, however, that the claimed peptides bind all integrins or to all cell types for the peptides to have the specified utility. In *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.* (1984), the Federal Circuit noted that "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid ... [I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." *Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569 (Fed. Cir.1984).

Rejection Under 35 U.S.C. § 102

Claims 1-6 were rejected under 35 U.S.C. § 102 (b) as being anticipated by Young et al. *Genomics* 7(4): 491-502 (1990) ("Young"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

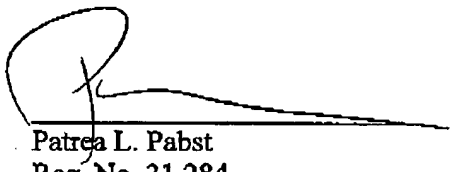
Claim 1 has been amended to recite "an active osteopontin peptide fragment". Support for this amendment can be found on page 11, lines 9-11 and page 12, lines 20-24. The term "fragment", which, according to the dictionary, means "a part broken off: an imperfect or incomplete part" (see attached copy of Webster's Third New International Dictionary), explicitly excludes **full-length** osteopontin. In addition, on page 12, lines 20-24, the specification states that an "active osteopontin peptide" includes one or more residues which differ from the amino acid residues present in a naturally occurring active osteopontin peptide. Young describes the deduced protein sequence of **full-length** osteopontin, and therefore, does not anticipate the claims as amended.

In addition, the Examiner has not provided any evidence that it would have been obvious for one of ordinary skill in the art to use a peptide fragment of osteopontin instead of full-length osteopontin, for example, to increase cell attachment to, or cell spread on, a biomaterial. The specification clearly illustrates the advantage of osteopontin fragments over full-length osteopontin in Table 8, which shows that the fragments are as effective, and in most cases, more effective, than naturally occurring osteopontin in increasing cell attachment and spreading.

If the Examiner is still not satisfied with the claim language, she is invited to have a telephone call with the Applicant's representative to discuss what she believes to be appropriate language.

Allowance of claims 1-3 and 5-6, as amended, is respectfully solicited.

Respectfully submitted,



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